The Cost-effectiveness of Pixantrone for Third/Fourth-line Treatment of Aggressive Non-Hodgkin's Lymphoma

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ABSTRACT

Purpose: Aggressive non-Hodgkin's lymphoma (aNHL) is associated with poor long-term survival after relapse, and treatment is limited by a lack of consensus regarding standard of care. Pixantrone was studied in a randomized trial in patients with relapsed or refractory aNHL who had failed ≥2 lines of therapy, demonstrating a significant improvement in complete or unconfirmed complete response and progression-free survival (PFS) compared with investigators' choice of single-agent therapy. The objective of this study was to assess the health economic implications of pixantrone versus current clinical practice (CCP) in the United Kingdom for patients with multiply relapsed or refractory aNHL receiving their third or fourth line of treatment.

Methods: A semi-Markov partition model based on overall survival and PFS was developed to evaluate the lifetime clinical and economic impact of treatment of multiply relapsed or refractory aNHL with pixantrone versus CCP. The empirical overall survival and PFS data from the PIX301 trial were extrapolated to a lifetime horizon. Resource use was elicited from clinical experts, and unit costs and utilities were obtained from published sources. The analysis was conducted from the perspective of the United Kingdom's National Health Service and personal social services. Outcomes evaluated were total costs, life-years, quality-adjusted life-years (QALYs), and cost per QALY gained. Deterministic and probabilistic sensitivity analyses were conducted to assess uncertainty around the results.

Findings: Pixantrone was estimated to increase life expectancy by a mean of 10.8 months per patient compared with CCP and a mean gain of 0.56 discounted QALYs. The increased health gains were associated with an increase in discounted costs of approximately £18,494 per patient. The incremental cost-effectiveness ratio of pixantrone versus CCP was £33,272 per QALY gained. Sensitivity and scenario analyses suggest that the incremental cost-effectiveness ratio was sensitive to uncertainty in the PFS and overall survival estimates and the utility values associated with each health state.

Implications: Pixantrone may be considered both clinically effective and cost-effective for patients with multiply relapsed or refractory aNHL who currently have a high level of unmet need. (*Clin Ther.* 2016;38:503–515) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: cost-effectiveness, non-Hodgkin's lymphoma, pixantrone, survival analysis.

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of diseases originating in various cells within the lymphoid system.[1] The clinical course of NHL ranges from indolent to aggressive, with diffuse large B-cell lymphoma (DLBCL) being the most common type of aggressive NHL (aNHL). DLBCL is usually diagnosed when the disease is widespread, with patients experiencing fever, fatigue, weight loss, and night sweats.[2]

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First-line chemotherapy for patients with DLBCL includes rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone.[1–5] However, ~50% to 60% of patients relapse within the first 2 years of treatment.[4] In as few as 10% of these patients, long-term survival with conventional salvage chemotherapies is achieved,[6] with the median survival after first relapse estimated at 4 to 6 months.[6] There is a lack of consensus with regard to standard of care, with no licensed therapies for patients with multiply relapsed or refractory NHL,[4] resulting in considerable unmet need for these patients.

Pixantrone is a novel aza-anthracenedione that was studied in a Phase III, multicenter, open-label, randomized trial in heavily pretreated patients with relapsed or refractory aNHL (ie, the PIX301 trial).[7] The efficacy and safety of pixantrone dimaleate provided at a dose of 50 mg/m^2 of active substance (or 85 mg/m^2) intravenously on days 1, 8, and 15 of a 28-day cycle, for up to 6 cycles, was examined compared with investigators' choice of single-agent therapy (vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, or gemcitabine) given at prespecified standard doses and schedules. Investigators' choice of treatments is consistent with current practice in England and Wales and is therefore referred to as current clinical practice (CCP) hereafter. Patients were followed up for 18 months after the last treatment for assessment of disease progression and survival. A significantly higher proportion of patients treated with pixantrone achieved a complete or unconfirmed complete response at the end of treatment versus those patients receiving the comparator drugs (20.0% vs 5.7%; $P = 0.021$). Progression-free survival (PFS) was significantly higher in the pixantrone group (hazard ratio, 0.60 [95% CI, 0.42–0.86]). Overall survival (OS) was not significantly longer (hazard ratio, 0.79 [95% CI, 0.53–1.18]), despite a favorable trend observed for pixantrone.[8]

As in numerous other countries, the United Kingdom's health care system requires that a new treatment be cost-effective; that is, the costs associated with a new treatment are balanced against its additional clinical benefits compared with currently used treatments. The objective of the present study was to assess the health outcomes and cost-effectiveness of pixantrone versus CCP over a lifetime for patients with multiply relapsed or refractory aNHL receiving third- or fourth-line treatment from the perspective of the UK National Health Service and personal social services.

MATERIALS AND METHODS

Model Design

A partition model was developed to estimate long-term clinical and economic outcomes for patients with multiply relapsed or refractory aNHL receiving third- or fourth-line treatment with pixantrone or CCP. CCP was assumed to comprise vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, and gemcitabine as included in the PIX301 trial.[7]

The model explored what might happen to a hypothetical cohort of patients by using a set of mutually exclusive health states: (1) stable/no progression, including progression-free patients; (2) progressive/relapsed disease, including living patients who have progressed; and (3) death. Patients can enter, remain in, or move ("transition") between health states (Figure 1). While in the stable/no progression health state, patients can stay on or discontinue initial treatment. The model cycle was set to 1 week (ie, patients can move between health states once weekly).

It was assumed that patients start in the stable/no progression health state on initial treatment. During each cycle, patients in the stable/no progression health state may remain stable and on initial treatment, or they may discontinue treatment. Alternatively, they can move to the progressive/relapsed health state or die. Patients in the progressive/relapsed health state can either remain in that state or die.

Patients were also at risk of experiencing adverse events (AEs) while on treatment in the stable/no progression state. AEs were modeled as events with cost and quality of life consequences. Treatment-emergent

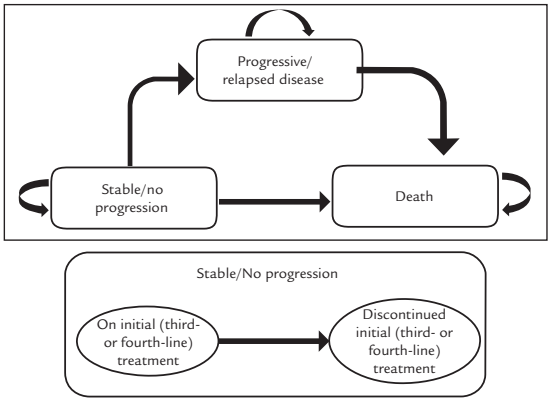

Figure 1. Model design.

grade 3 and 4 AEs occurring in at least 5% of the patient population and grade 2 AEs considered important by clinical experts were included because these were the AEs believed to have an impact on quality of life and/or health care resource use.

This approach is appropriate for modeling chronic disease when patients pass through a series of clearly defined and mutually exclusive health states based on the treatment and progression. Furthermore, it has the ability to reflect time-dependent parameters such as PFS and OS through the use of survival curves following the disease progression in this patient population. By calculating the area under the survival curves in each cycle, the distribution of the patient cohort between the different health states defined by these curves can be estimated. The model structure was validated by comparing it with earlier models[8–11] that adopted a similar 3 health state structure, and also with input from clinicians active in the area (in accordance with modeling guidelines).[12]

Model Inputs

Efficacy and Safety Inputs

The likelihood of moving between different health states was estimated by using area under the curve or partition approach facilitated by PFS and OS curves from the PIX301 trial.[7] Because OS and PFS were not fully observed, results were extrapolated by using survival functions that best fit the patient-level data in accordance with current guidelines.[13–15] Fits using exponential, Weibull, lognormal, log-logistic, and generalized gamma distributions were assessed graphically by using parametric plots and with fit statistics, including the Akaike and Bayesian information criteria (Table I). The predicted OS and PFS were also assessed by clinical experts for external validation by comparing these rates with the survival pattern seen in clinical practice and determining if they make sense clinically and biologically.[14,16] The best fit that was deemed clinically plausible was the lognormal distribution, separately fitted to each arm; this technique was subsequently used in the model base-case (Figure 2). The Weibull distribution provided the worst fit; however, due to its common use in oncology models,[17] sensitivity analysis was conducted on this and other distributions that provided a reasonable fit.

Discontinuation of the initial line of treatment for each arm by weekly cycles was obtained from the PIX301 trial.[7] Similarly, the risk and duration of AEs were also obtained from the PIX301 trial.

Utilities

In absence of utility data from the PIX301 trial and in the literature specific to the modeled population, patients' quality of life (based on expert opinion) was assumed to be similar to that of patients with second-line advanced and/or metastatic renal cell carcinoma.[18] A pre-progression utility of 0.76 (SE, 0.03) and post-progression utility of 0.68 (SE, 0.04) were therefore used for the base-case analysis. Sensitivity analysis was conducted by using alternative utility values as obtained from the published literature, including values for

Table I. Statistical fit criteria for overall survival and progression-free survival.

	Overall Survival				Progression-free Survival			
	Pixantrone Arm		Current Clinical Practice Arm		Pixantrone Arm		Current Clinical Practice Arm	
Distribution	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	150.530	154.354	152.149	155.933	159.164	162.988	150.382	154.166
Lognormal	147.214	151.038	148.035	151.819	150.907	154.731	150.358	154.142
Log-logistic	148.556	152.380	149.051	152.834	152.022	155.846	144.687	148.471
Generalized gamma	148.607	154.343	149.636	155.312	150.601	156.337	149.399	155.074
Exponential	149.103	151.015	150.823	152.714	157.649	159.561	148.382	150.274

AIC = Akaike information criterion; BIC = Bayesian information criteria.

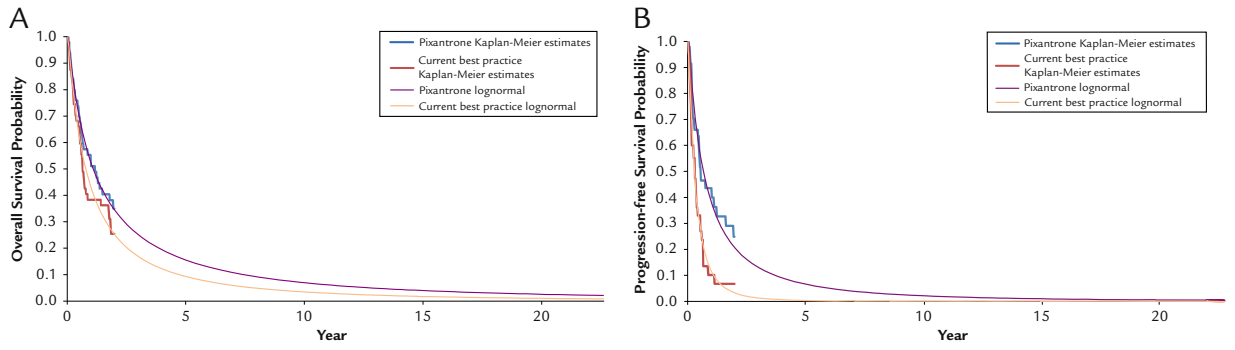

Figure 2. (A) Overall survival and (B) progression-free survival for patients with multiply relapsed or refractory aggressive non-Hodgkin's lymphoma (estimated from Kaplan-Meier and separately fitted lognormal distributions from post-hoc analyses of the PIX301 trial).

patients with chronic myeloid leukemia,[19] chronic lymphocytic leukemia,[20] metastatic melanoma,[21] follicular lymphoma,[3,22,23] renal cell carcinoma,[24] and DLBCL.[25] Utility decrements associated with AEs were obtained from the published literature[26–33] and were applied for the duration observed in the PIX301 trial. The weighted average annual utility decrements associated with grade 2 AEs experienced with pixantrone and CCP were calculated to be 0.0075 and 0.0066, respectively. The average utility decrement associated with grade 3/4 AEs experienced with pixantrone and CCP were calculated to be 0.0078 and 0.0073.

Resource Use and Costs

Drug costs were obtained from the Electronic Market Information Tool (eMIT),[34] which provides information about prices and usage for generic drugs and pharmaceutical products in the United Kingdom, and from the British National Formulary.[35] If >1 brand was available, the least expensive option was selected. Drug costs were applied assuming that vial sharing is not common practice for any treatment due to low patient numbers (as advised by clinicians) (Table II). Calculation of drug costs including wastage in the absence of vial sharing was conducted by using the suggested method of Sacco et al.[36] In addition to the cost of chemotherapies, a cost of administration was applied to each treatment according to the length and timing of administration as specified by healthcare resource groups (HRGs).[37]

Resource use associated with disease management and the treatment of AEs was elicited from 3 UK clinical experts. Specific resource use items included health care professional contacts, subsequent therapies, laboratory tests and imaging, inpatient stay, and personal and social services (residential care, day care, home care, and hospice). Disease management was estimated separately for patients in stable/no progression state on active treatment, stable/no progression state off active treatment, and progressive disease. Unit costs were obtained from the National Schedule of Reference Costs,[37] the British National Formulary,[35] Personal Social Services Research Unit,[38] and National Audit Office, reported in 2011–2012 prices (Table II).

Analyses

The analyses observed patients throughout their lifetimes, estimated to be a maximum of 23 years using the average life expectancy in the United Kingdom in the general population[39] for the average age of the patients entering the PIX301 trial. Outcomes were estimated by calculating the life-years gained, quality-adjusted life years (QALYs) gained, and costs accumulated over the time horizon of the model per patient. Costs and health benefits were discounted at an annual rate of 3.5%.[13] The relative benefit of pixantrone versus CCP was assessed by using the incremental cost-effectiveness ratio (ICER), which represented the additional cost required to achieve an additional QALY with pixantrone compared with CCP. The effect of uncertainties associated with the model assumptions and input parameters on model outcomes was assessed by a combination of

Table II. Key drug and disease management costs.

Description	Units	Price/Cost, £	Source
Drug costs			
Vinorelbine	10 mg/mL; 1-mL vial	5.83	34
	10 mg/mL; 5-mL vial	21.83	34
Oxaliplatin	50-mg vial	12.23	34
	100-mg vial	21.46	34
Ifosfamide	1000-mg vial	43.53	35
	2000-mg vial	88.62	35
Ifosfamide	50-mg capsule	4.99	35
	100-mg capsule	8.72	35
Etoposide (100 mg IV)	20-mg/mL; 5-mL vial	2.09	34
	20-mg/mL; 25-mL vial	7.98	34
Mitoxantrone	2-mg/mL; 10-mL vial	26.06	34
	2-mg/mL; 13-mL vial	26.96	34
Gemcitabine	200-mg vial	3.22	34
	1000-mg vial	12.64	34
	2000-mg vial	24.70	34
Pixantrone	50-mg vial	553.50	35
Administration costs			
Oral chemotherapy (applied to etoposide 50 mg)	Per administration	163.00	8
Simple parenteral chemotherapy at first attendance (applied to pixantrone, vinorelibine, etoposide 100 mg, mitoxantrone, and gemcitabine)	Per administration; 30 minutes' nurse time, 30–60 minutes' chair time	231.00	8
Complex chemotherapy, including prolonged infusional treatment at first attendance (applied to ifosfamide and oxaliplatin)	Per administration, 60 minutes' nurse time, >2 hours' chair time	302.00	8
Deliver subsequent elements of a chemotherapy cycle	Per administration	206.00	8
Costs associated with stable/no progression health state while on initial treatment			
Professional and social services	Per 4 weeks	476.42	38
Health care professional costs	Per 4 weeks	788.96	38, 47
Treatment follow-up costs	Per 4 weeks	86.63	47
Hospital costs	Annual	2357.28	38, 47
Grade 2 AE costs with pixantrone	Average cost* per AE	39.65	24, 35, 37
Grade 2 AE costs with CCP	Average cost* per AE	43.18	24, 35, 37
Grade 3/4 AE costs with pixantrone	Average cost* per AE	254.26	24, 35, 37
Grade 3/4 AE costs with CCP	Average cost* per AE	385.78	24, 35, 37
Costs associated with stable/no progression health state while discontinued initial treatment			
Professional and social services	Per 4 weeks	119.10	38
Health care professional costs	Per 4 weeks	220.38	38, 47
Treatment follow-up costs	Per 4 weeks	86.63	47
Subsequent treatment costs	One off/on discontinuation	1169.06	34, 35

(continued)

Table II. (continued).

Description	Units	Price/Cost, £	Source
Costs associated with progressive/relapsed health state			
Professional and social services	Per 4 weeks	1993.89	38
Health care professional costs	Per 4 weeks	990.74	38, 47
Treatment follow-up costs	Per 4 weeks	18.44	47
Subsequent treatment costs	One off/on progression	1723.68	34, 35
Hospital costs	Annual	1982.03	38, 47
Progression costs	One off on progression	798.20	35, 38

AE = adverse event; CCP = current clinical practice.
*Based on a weighted average of distribution of AEs and cost per each AE. Cost does not reflect variations in incidence.

deterministic 1-way sensitivity analyses, subgroup analyses, scenario analyses, and probabilistic sensitivity analysis (PSA).

A 1-way deterministic sensitivity analysis was performed in which each parameter was varied according to its 95% CI or SE, where reported, while holding all other parameters constant. The parameters varied included OS, PFS, treatment discontinuation, risk of AEs, utilities, drug costs, administration costs, disease management costs, and AE-related costs.

To assess whether the base-case results are generalizable across various populations with different characteristics and to assess uncertainties associated with the trial population, subgroup analyses were conducted. We examined a subgroup of patients who were classified as having aggressive disease by an independent central review (ICR), and among those, a subset of patients who had received rituximab previously.

Scenario analyses were also performed to examine the impact of structural and input uncertainties on model outcomes. Each scenario was formulated by using different assumptions for extrapolation of OS and PFS, including use of Kaplan-Meier estimates until trial follow-up, generalized gamma (providing the best statistical fit), and Weibull (the most commonly used) distributions. In addition, use of alternative utility value sets was tested, as well as use of shorter time horizons.

Finally, a PSA was undertaken to gain a better understanding of the effect of parameter uncertainty. Inputs were assigned a probability distribution and varied simultaneously 5000 times, with each simulation producing a pair of incremental QALYs and costs. PFS, OS, treatment discontinuation, costs, and utilities were varied simultaneously and independently of each other. Time horizon, discount rates, and drug costs were excluded from the PSA because they are not subject to parameter uncertainty. Distributions for each parameter were assigned in accordance with guidelines on representing parameter uncertainty[40,41]; that is, a gamma distribution was applied to the costs, the length of AEs, and the number of AEs; a normal distribution for body surface area; a β-distribution for utilities; and a Dirichlet distribution for subsequent treatments. For the OS and PFS distribution parameters, a Cholesky decomposition of the covariance matrix was used[40] to maintain correlation between parameters.

RESULTS

Base-case Analysis

In the base-case analysis, pixantrone was more effective compared with CCP, increasing life expectancy by a mean of 10.8 undiscounted months per patient (33.96 vs 23.16 months). The gain in life expectancy was primarily observed in the progression-free state, which subsequently resulted in a discounted incremental QALY of 0.56 (1.76 QALYs for the pixantrone arm; 1.20 QALYs for CCP) (Table III).

Mean discounted costs incurred over the lifetime time horizon among patients receiving pixantrone were £84,703 per patient, £18,494 higher than patients receiving the comparator treatments. Increased costs were primarily attributed to increased drug acquisition and administration costs, as well as

increased costs of care in the pre-progression state, due to extended pre-progression survival. However, these were accompanied by cost savings in the progressed health state. The increase in both costs and QALYs led to an ICER of pixantrone versus CCP of £33,272 per QALY gained.

Sensitivity Analyses

Results from the 1-way sensitivity and scenario analyses highlighted that the ICER was most sensitive to variation in the PFS and OS estimates and the utility value for the stable/no progression health state. Variation in disease management costs and AE-related costs had a smaller influence on the ICER compared with PFS, OS, and utility estimates, and did not alter the base-case conclusions. The ICERs observed in the subgroup analyses were £35,326 per QALY gained in patients classified by ICR, and £45,282 per QALY gained in patients classified by ICR who had received prior rituximab (Table IV). Different assumptions regarding the extrapolation varied the ICER between £2,468 per QALY (generalized gamma) and £40,890 per QALY (Weibull). Use of alternative utility value sets resulted in ICERs ranging from £29,419 to £36,961 per QALY.

The cost-effectiveness plane of the PSA highlights that the majority of simulations were in the north-east quadrant, suggesting that pixantrone was both more costly and more effective than the comparator (Figure 3). Approximately 41.50% and 83.12% of simulations resulted in pixantrone being cost-effective at a threshold of £30,000 and £50,000, respectively, per QALY gained.

Table III. Base-case results.

Variable	Pixantrone	Current Best Practice
Drug and administration costs, £	16,843	316
AE costs, £	371	285
Pre-progression costs, £	17,282	6542
Post-progression costs, £	45,145	54,620
Total costs, £	79,650	66,209
Total LYG	2.42	1.71
Total QALYs	1.76	1.20
Incremental costs, £	18,494	
Incremental LYG	0.71	
Incremental QALYs	0.56	
ICER (QALYs), £	33,272	

AE = adverse event; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted LY.

DISCUSSION

This study assessed the cost-effectiveness of pixantrone versus CCP for the treatment of patients with multiply relapsed or refractory aNHL. The analysis expanded on the findings from the PIX301 trial,[7] providing estimates on the mean gain in life expectancy over a lifetime time horizon in patients treated with pixantrone. Our analysis estimated that pixantrone-treated patients experience longer life expectancy by a mean of 10.8 months (undiscounted). This mean estimate differs from the median gain in life expectancy reported in the PIX301 trial (2.6 months)[7] as it describes the mean expected health gain of all patients' complete life expectancy as requested by National Institute for Health and Care Excellence (NICE) guidelines. Because the trial data were collected over 18 months of follow-up, patients' complete life expectancy data were not available. Based on the Kaplan-Meier estimates, 35% and 25% of pixantrone- and CCP-treated patients were alive by the end of follow-up, respectively. PFS and OS were therefore extrapolated by using parametric survival analyses according to guidelines from the NICE Decision Support Unit.[14] Findings of a higher mean versus median gain in life expectancy are common in oncology modeling.[42,43] This outcome can be attributed to patients remaining alive even after study follow-up and a proportion of patients experiencing longer life expectancy. Because the median omits the additional life expectancy beyond study follow-up, the potential full benefits are not incorporated.[19,43]

The predicted OS gain with pixantrone primarily occurred pre-progression, which reduces the uncertainty associated with the analysis, as a bigger proportion of time pre-progression is usually measured within the trial, while time post-progression requires

Table IV. Scenario analysis results.

Description of Data Sources	ICER (£/QALY), Discounted
Alternative utility scenarios (Base case: pre-progression,0.76; post-progression, 0.68)	
Pre-progression 0.85, post-progression 0.73 (CML, second-line for dasatinib, nilotinib, and imatinib)[20]	29,419
Pre-progression 0.65, post-progression 0.47 (CLL, third-line for ofatumumab)[20]	36,961
Pre-progression 0.80, post-progression 0.76 (metastatic melanoma, second-line metastatic)[53]	32,151
Pre-progression 0.78, post-progression 0.62 (follicular lymphoma, first-line maintenance for rituximab)[3,21,23]	31,452
Pre-progression 0.70, post-progression 0.59 (renal cell carcinoma, first-line metastatic for pazopanib)[24]	35,561
Pre-progression 0.81, post-progression 0.6 (DLBCL, first- and second-line for CHOP and R-CHOP)[25]	29,804
Population of subgroups (base-case: ITT third- and fourth-line)	
Patient treated with third- or fourth-line, histologically confirmed by ICR	35,326
Patient treated with third- or fourth-line, histologically confirmed by ICR, who had received previous rituximab	45,282
Distribution used for OS and PFS (base case: lognormal distribution)	
Kaplan-Meier estimates followed by lognormal distribution	27,375
Generalized Gamma distribution	2,468
Weibull distribution	40,890
Time horizon	
5-year	35,347
10-year	31,905
PAS	24,181

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; DLBCL = diffuse large B-cell lymphoma; ITT = intention-to-treat; ICER = Incremental cost-effectiveness ratio; ICR = independent central review; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; QALY = quality-adjusted life year; R-CHOP = CHOP plus rituximab.

extrapolation. This finding contrasts with those of many other oncology drugs for which the majority of the benefit is estimated to be post-progression.[44,45] This finding is, however, supported by previous economic models of treatments in hematology, which reported on treatments to increase life expectancy in a better health state, usually pre-progression.[46,47] Increased life expectancy in a better health state may be correlated with a significantly higher proportion of pixantrone-treated patients achieving complete and unconfirmed complete response in the PIX301 trial.[7]

The increased health benefits observed for pixantrone were accompanied by increased costs, mainly higher drug acquisition and pre-progression costs (including administration) that were partly due to the added cost of pixantrone and partly because the delayed progression required longer disease follow-up. However, due to the gain in life expectancy being primarily pre-progression, there was a small cost offset in the postprogression state, during which costs are usually higher.

The estimated ICER of £33,272 per QALY gained is lower than ICERs typically estimated for life-extending

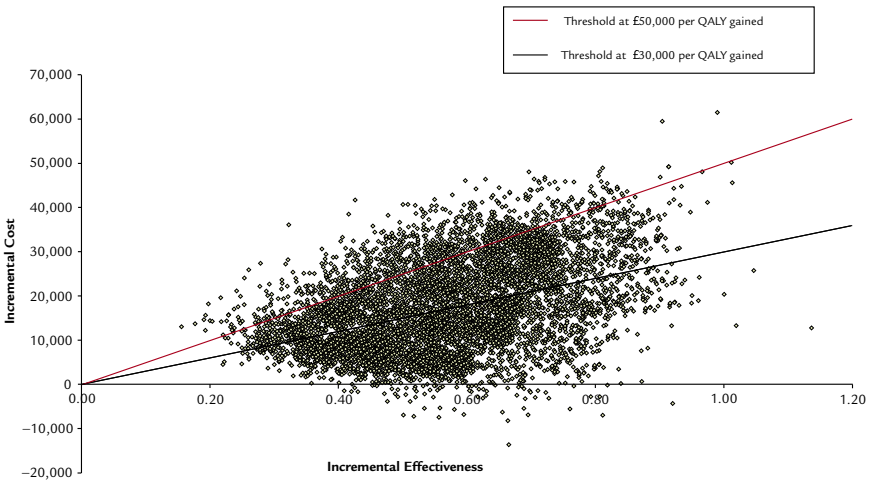

Figure 3. Cost-effectiveness plane: pixantrone versus current clinical practice. Each of the dots in the scatterplot represents a pair of incremental costs and incremental quality-adjusted life-years (QALYs) for pixantrone versus current clinical practice as generated by the probabilistic sensitivity analyses. For observations that fall to the right of the solid lines, pixantrone is a cost-effective alternative at the specified threshold.

treatments in the United Kingdom. The commonly used threshold for these type of treatments has been £50,000 per QALY gained (higher than the standard threshold of £20,000–£30,000 per QALY) if the following criteria are met: (1) the treatment is indicated for patients with a short life expectancy (<24 months); (2) it extends life by at least 3 months compared with current National Health Service treatment; (3) it is licensed or indicated for small patient populations; and (4) estimates are considered plausible, objective, and robust.[48] Although the first 3 criteria are met by pixantrone due to the small patient population, uncertainty in the estimates play an important role. If considered under the end-of-life criteria, pixantrone is highly cost-effective. In the United Kingdom, there is also a patient access scheme (PAS) in place for pixantrone, which decreased the estimated ICER to £24,181 per QALY gained.[49] With the PAS in place, pixantrone was cost-effective at the commonly adopted UK threshold of £20,000 to £30,000 per QALY gained.

The model included in the study was used in the technology appraisal of pixantrone by NICE, and it received a positive recommendation.[49] The ICER estimated in the base-case analysis of this study differs from that reported in the final NICE appraisal, in which the cost-effectiveness estimate was limited to patients with an ICR-confirmed diagnosis who were receiving third- or fourth-line treatment and had previously received rituximab. The rationale for using this subset of patients was based on several factors as identified by NICE during the appraisal.[50] It was believed that most patients treated in the United Kingdom would receive rituximab before the third- or fourth-line treatment, whereas in the PIX301 study, only 55% of patients received prior rituximab (it only became available for this indication during the study in some countries and was not available in all regions).[7] In addition, NICE limited the population to patients who were confirmed to have aggressive disease by an ICR, despite all patients in the PIX301 trial being histologically confirmed on-site for aggressive disease. Classification of the lymphoma according to retrospective ICR was not conducted in all patients because there was either no sample or insufficient sample for this assessment.[7] Our analysis focused on the intention-to-treat population receiving third- or fourth-line treatment, consistent with the European licensing for pixantrone.[51] However, a subgroup analysis was conducted to assess these assumptions and aid in the projection of the health economic benefits of pixantrone across populations. Limiting the patient population to those who were confirmed

by ICR increased the ICER by 6% compared with the base-case. Additional subgroup analysis on patients with previous rituximab experience suggested an additional 28% increase in the ICER to £45,282 per QALY gained. The ICER from this subgroup had a higher uncertainty due to the smaller patient population; however, both scenarios resulted in an ICER below the threshold of £50,000 per QALY gained and below £30,000 per QALY gained when the PAS was considered by NICE.

As with all economic evaluations, our analysis is subject to a number of limitations. The PIX301 trial was considered to represent the best available evidence to assess pixantrone.[7] However, due to the small multiply relapsed aNHL patient population eligible for systemic treatment and the resulting slow accrual of patients, a relatively small sample size (140 randomized patients) was available for the comparison of pixantrone monotherapy versus other single chemotherapy agents in third and subsequent lines of treatment. Although this factor is an important source of uncertainty in the evaluation, this was reflected in the PSA by varying clinical parameters obtained from the PIX301 trials based on their variance–covariance matrices. The PSA results suggest pixantrone had the highest probability of being cost-effective at thresholds of £35,000 per QALY gained and higher. In addition, the comparator arm in the PIX301 trial was assumed to represent clinical practice, an assumption that was validated with UK clinicians. This finding may not be generalizable to all settings, however, given the lack of consensus among clinicians regarding third and subsequent lines of therapy.

Other limitations and areas of future research stem from the paucity of data specific to this population. Relevant health-related quality of life data were not available in the PIX301 trial or in the published literature; as a result, these data in patients with advanced and/or metastatic renal cell carcinoma treated with second-line agents[18] were used in this study, as accepted by the NICE Appraisal Committee.[50] However, scenario analyses with a range of utility value sets did not alter the conclusions of the analysis. In addition, a recent economic evaluation in patients with relapsed or refractory aNHL, which used the Functional Assessment of Cancer Therapy–General quality-of-life instrument to derive utilities, found that the utility varied from 0.801 to 0.705 from baseline and after 2 cycles of chemotherapy.[52] A weighted average of these values results in a utility value of 0.765, consistent with our base-case utility estimate of 0.76, indicating that the utility value used in the model was reasonable.

CONCLUSIONS

To the best of our knowledge, this study is the first to assess the cost-effectiveness of pixantrone and extrapolate the PIX301 results[7] to provide estimates of mean overall gain in life expectancy. Furthermore, it is the first study to examine the health and economic effects of treatments in patients with multiply relapsed or refractory aNHL from the perspective of the UK National Health Service. The analysis shows that pixantrone may be considered to be both a clinically effective and a cost-effective treatment for patients with multiply relapsed aNHL, a disease with a high level of unmet need.

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All authors approved the final article.

CONFLICTS OF INTEREST

Ms. Muszbek, Lanitis and Dr. Kadambi were employees of Evidera and Dr. Hatswell was an employee of BresMed Health Solutions at the time the study was conducted. Both Evidera and BresMed received funding from Science Union et Cie and Cell Therapeutics in connection with conducting this study and with the development of the manuscript. Drs. Wang, Singer, and Pettengell were employees of Cell Therapeutics at the time the study was conducted. Dr. Pettengell received honorarium from Cell Therapeutics. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

N. Muszbek has led the model conceptualization, the data acquisition and analyses, interpretation of results, reviewed the model programing and participated in the writing of the manuscript. A. Kadambi has co-led the model conceptualization, the data acquisition and analyses, interpretation of results. T. Lanitis has done the programming of the model and has participated in the model conceptualization, the data acquisition and analyses, interpretation of results and led the writing of the manuscript. A.J. Hatswell has participated in the data acquisition and interpretation of results. D. Patel has participated in the model conceptualization, validation of data and interpretation of results. L. Wang and J.W. Singer participated in the model conceptualization and interpretation of results, and have done the post-hoc analyses of the trial data. R. Pettengell has participated in the validation of model concept, data analyses and the interpretation of results. All authors have reviewed and commented on the manuscript. The sponsors were not involved in the writing of the manuscript.

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